American Journal of Medical Genetics 62:113–119 (1996)

Recognizing Ullrich-Turner Syndrome by Discriminant Analysis of Craniofacial Structure

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In the present paper, we propose an efficient strategy for identification of craniofacial anomalies in the Ullrich-Turner syndrome (UTS). Standardized portrait- and profile-photographs were taken of 21 UTS patients with X-monosomy and 21 normal females. Twenty-seven craniofacial parameters were read from the photographs. The data were analyzed by discriminant analysis, a multivariate statistical method. The result was a function represented by a linear combination of all those craniofacial parameters which best separate the two groups. The discriminant function was applied to 15 additional patients with UTS of various cytogenetic types. All 15 patients were classified correctly.

The technique facilitates syndrome-recognition and is a contribution toward the study of karyotype-phenotype relations.

KEY WORDS: Ullrich Turner syndrome, craniofacial anomalies, X-monosomy, standardized photography, discriminant analysis

INTRODUCTION

In the present paper, we discuss an efficient strategy for the identification of craniofacial anomalies in the Ullrich-Turner syndrome [Turner, 1938; Ullrich, 1930]. Craniofacial parameters [Karolyi, 1971; Stengel-Rutkowski et al., 1984] are used to separate an UTS patient group from a group of young healthy females by means of discriminant analysis. This method had previously been applied successfully to the corresponding problem with a group of Down syndrome patients [Schüllermann, 1986; Allanson et al., 1993].

Received for publication January 10, 1995; revision received September 29, 1995.

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METHOD

Summary of Procedure

Figure 1 shows the various steps of our method. Portrait- and profile-photographs of 21 patients with UTS and of 21 normal females of nearly the same age were taken under standardized conditions [Kaiser, 1988]. The values of 27 craniofacial parameters were read from these photographs. Standardization by forming ratios finally yielded 29 parameters entering the analysis. The data were analyzed in a simultaneous fashion by discriminant analysis, a multivariate statistical method [Fisher, 1938; Armitage et al., 1987; Flury et al., 1983]. The results of this analysis are a function represented by a linear combination of all those craniofacial parameters which allow an optimal diagnostic differentiation between UTS patients and normal females. In other words, the discriminant analysis identifies those craniofacial parameters which—linked together in the resulting discriminant function—are those which optimally separate the two groups.

Photographic Conditions

All the photos were made in the photo lab of the Frankfurt University Children's Hospital (Universitäts-Kinderklinik Frankfurt am Main). The subjects sat upright on a chair in front of a white background. The exact positions of the lights, the chair and the tripod during each photo session were marked on the floor. Figure 2 shows the positions and distances during the photo sessions.

For the portrait shots the subjects were asked to look directly into the camera with their mouths closed. Their hair was combed back to keep their faces and ears clear. The view-finder in the camera had coordinates to check the position of the head in relation to the position of the camera. The lightning was shadowless.

The photos were all taken on Ilford XP1 black and white negative film. All films used had the same emulsion number to exclude any material scattering. The focus level was at eye level for the portrait shots, and for the profile shots it was at the level of the lateral left corner of the eye. The distance between the focus level and the film level was about 0.7 m. The correct shutter speed was established by taking test shots and exposing a gray card. Using 200 ASA and a 5.6 lens it was 1/125 sec.

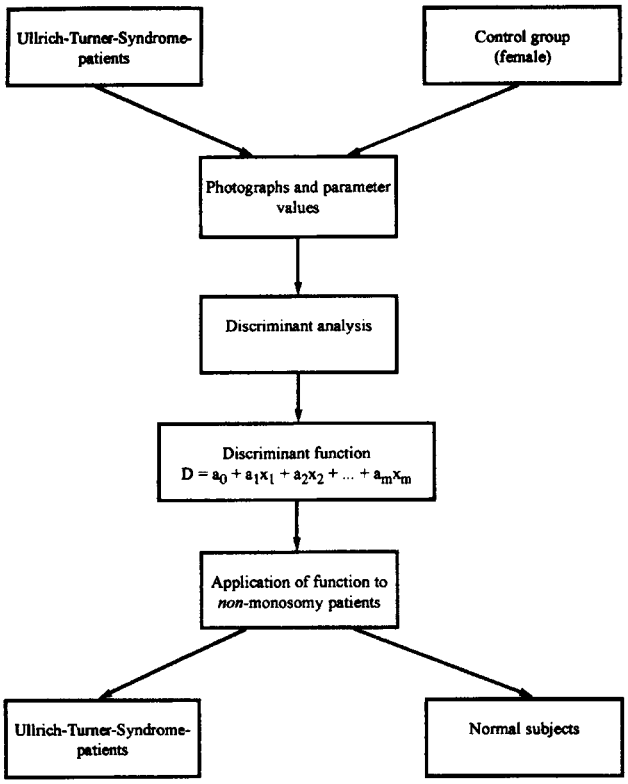

Fig. 1. Procedure of analysis.

When developing each single shot a constant distance between the inner corners of the eyes was chosen. Because the measurements from the single photos were not used in an absolute but in a standardized manner for the discriminant analysis, there is no loss of information by using a constant distance between the inner eye corners as photographic standard.

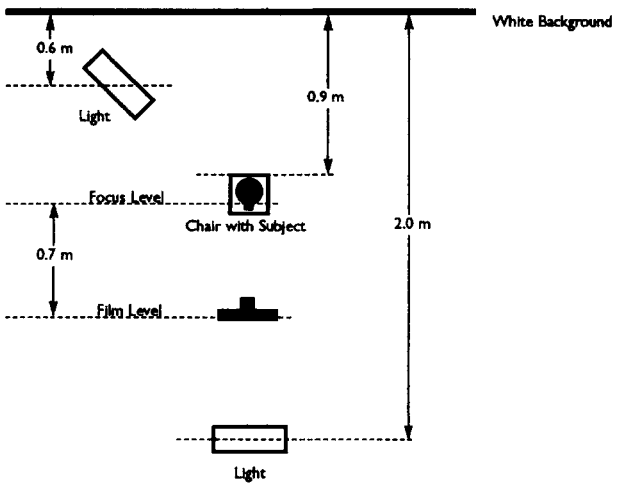

Fig. 2. Positions and distances during the photo sessions.

TABLE I. Age Distributions

Group	n	Age (years) Range	Average	Median
X-monosomy UTS	21	7–21	14.05	15
Control group	21	7–20	14.76	16
Non-classical UTS	15	12–20	15.53	16

Subject Selection

The author photographed 57 subjects from the ages of 7 to 21 years. The age group distribution is included in Table I. Two standard photographs, one portrait and one profile, were made of each subject. Of the 57 subjects involved, 36 were patients with an UTS and 21 were healthy.

All 36 girls and women with an UTS were patients at the Endocrinology Ward of the Frankfurt University Children's Hospital. The group was divided into 21 patients with an X-monosomy and 15 non-classical UTS patients. In all UTS patients the diagnosis was verified by genetic analysis. Table II shows the karyotypes and ages of the 15 non-classical UTS patients.

The 21 subjects in the control group were not known to the authors before the day of their photo sessions. They were not being treated in any way by the Pediatric or Endocrinology Wards. Therefore, an unconscious preference of certain types of subjects was not possible. The criteria for the selection process of the control group was body size, which had to be within the mid-average areas of each age group. Besides that, subjects with any sign of developmental problems were excluded. All subjects were of white race. The older members of the control group were asked when menarche had occurred to prevent taking a subject into the control group with an undetected UTS. Other criteria for matching were not considered as reasonable because of the vast psycho-social deficits and retardations arising from a syndrome associated with considerably decreased body size, sexual infantilism, and infertility. We did not want to shift the control group to any deletive level in order to avoid preselection of any kind.

TABLE II. Karyotypes and Ages of 15 Non-Classical UTS Patients

n	Karyotype	Age (years)
1	45,X0/47,XXX	14
2	45,X0/47,XXX	13
3	45,X0/47,XXX	14
4	45,X0/46,XX	12
5	45,X0/46,XX	15
6	45,X0/46,XX	12
7	45,X0/46,XX	20
8	46,XX/46,X,i(Xq)	18
9	45,X0/46,X,i(Xq)	17
10	46,X,i(Xq)	16
11	46,X,i(Xq)	18
12	46,X,i(Xq)	19
13	46,X,i(Xq)	18
14	46,X,i(Xq)	13
15	46,X,del(Xp)	19

Data Recording and Data Processing

The age distributions of both groups were compared by the Wilcoxon test showing no significant difference.

All craniofacial parameters taken from the portrait and profile photographs are listed in Tables III–VI and Figs. 3–6. The measurements were made using a ruler and protractor.

The large variability between subjects of facial measurements made it appear advisable not to let the measured values enter directly the discriminant analysis. The use of ratios of the measurements instead yields information about the more important craniofacial proportions of the faces. These ratios, which are interpretable as a *standardization,* were defined separately for portrait and profile measurements.

Additionally the following parameters were defined:

- ratios $Q_1, \ldots, Q_4$ to express the proportions of widths to heights:

$$Q_1 = \frac{B_1}{H_1}$$

$$Q_2 = \frac{B_1}{H_2}$$

$$Q_3 = \frac{AB_1}{H_1}$$

$$Q_4 = \frac{AB_1}{H_2},$$

- ratio *NHG,* giving a measure of the elevation of the nose baseline:

$$NHG = \frac{NL}{N_2},$$

- ratio *NP,* representing the prominence of the nose:

$$NP = \frac{NL}{V},$$

- ratio *OP,* representing the prominence of the upper jaw:

$$OP = \frac{SR}{NR},$$

- ratio *KP,* representing the prominence of the chin:

$$KP = \frac{KR}{NR}.$$

TABLE III. Definition of Heights in the Portrait Photographs

Abbreviation	Definition: distance
H_1	Endocanthion—Gnathion
H_2	Endocanthion—Lip fissure
H_3	Lip fissure—Gnathion
NH	Endocanthion—Subalare
OH	Subalare—Upper edge of upper lip
LH	Upper edge of upper lip—Lower edge of lower lip
KH	Lower edge of lower lip—Gnathion

TABLE IV. Definition of Widths in the Portrait Photographs

Abbreviation	Definition: distance
B_1	Bizygomatic diameter
B_2	Bigonial diameter
LB	Lip-width, e.g., right to left cheilion
NB	Bialare diameter
AB_1	Right to left exocanthion
AB_2	Average between right and left width of palpebral fissure

Table VII gives a list of all 29 parameters—20 portrait parameters and 9 profile parameters—which eventually entered the analysis.

Discriminant Analysis

The discriminant analysis estimates the constants $a_0, a_1, \ldots, a_m$ of the linear model *D:*

$$D = a_0 + a_1 x_1 + a_2 x_2 + \ldots + a_m x_m.$$

The estimate of *D,* denoted by *D,* may contain parameters which do not contribute significantly to the optimal separation of the two groups of 21 patients and 21 normal females. Therefore, so-called stepwise procedures were applied [SPSS, 1986] to reduce the number of parameters in the model so that the resulting "significant model" $\hat{D}^*$ will contain only those parameters which do contribute significantly to the separation. Mathematical details are discussed in the Appendix.

RESULTS

The step-down analysis (see the Appendix) resulted in the following discriminant function, consisting of 9 variables out of the 29:

$$\begin{aligned}\hat{D}^* = {} & -6.489 + 25.711 \cdot NH - 14.612 \cdot B_1 \\ & + 14.387 \cdot B_2 - 25.029 \cdot AB_2 + 0.210 \cdot W_3 \\ & - 27.359 \cdot N_2 + 23.778 \cdot NL - 3.601 \cdot NP \\ & + 11.388 \cdot OP.\end{aligned}$$

The separation by D^* was perfect: all 42 females were correctly classified.

Because of equal sample sizes in the two groups (n = 21 each), inserting measurements in $\hat{D}^*$ from any patient with UTS gives a negative $\hat{D}^*$. A positive $\hat{D}^*$ results from measurements taken from normal females. Therefore, the sign of D^* can be used as the criterion for the classification as UTS patient or normal female.

The step-up analysis resulted in only five variables contained in the model which also yields perfect separation between the UTS-group and the control group.

TABLE V. Definition of Angles in the Portrait Photographs

Abbreviation	Definition
W_1	Angle of the eyes
W_2	Angle of right and left lower jaw tangents
W_3	Angle of right and left zygomatic-gonial straight-lines

TABLE VI. Definition of Parameters in the Profile Photographs

Abbreviation	Definition: distance
N_1	Nasion—Stomion
N_2	Nasion—Subalare
NL	Nasion—Pronasale
V	Pronasale—Profile-line
NT	Nasion—Profile-line
AT	Exocanthion—Profile-line
OR	Incisura ant. of the ear—Ophryon
NR	Incisura ant. of the ear—Nasion
SR	Incisura ant. of the ear—Subalare
KR	Incisura ant. of the ear—Gnathion
OL	Incisura ant. of the ear—Exocanthion

The five variables were *NH*, AB_2, *NT*, *NHG*, and *NP*, three of which (*NH*, AB_2, and *NP*) are contained in the larger model of nine variables also. However, when applying this model to the discrimination between the control group and the group of 15 additional subjects with UTS but without X-monosomy, 6 of the 15 subjects were misclassified as normal. Using instead the model containing the nine variables resulting from the step-down analysis all 15 subjects were classified as UTS, independently of their individual chromosomal constellations (Figs. 7, 8). Insofar the model with the nine variables is confirmed by a second discrimination using another group of subjects.

The fact that both UTS groups (the X-monosomy patients and the group with other chromosomal abnormalities that can cause UTS) were classified correctly by the model from the step-down analysis shows that the nine variables selected out of all 29 variables are perfectly discriminative when they are considered simultaneously in the discriminant function. We prefer this model to one which contains fewer variables and is easier to use but lacks the advantage of 100% discrimination.

The absolute values of the standardized canonical discrimination coefficients (see the Appendix) vary between 0.74 (*NH*) and 1.09 (B_2) in the model with nine variables except for the variable *OP* with a value of 0.35, that is, eight variables are of about equal importance for the separation of the UTS patients and normal females. The overall discrimination shows *Wilks' lambda* = 0.146. In the model with five variables, four are of about equal importance; their absolute values vary between 0.66 and 0.87 except for *NT* with a value of 0.32; *Wilks' lambda* is 0.171. That is, the model with nine variables is the better discriminatory one and documents another time that in general step-down procedures are superior to step-up procedures.

In patients with UTS (X-monosomy), the averages of the craniofacial parameters B_1, B_2, and AB_2 are larger than those of the control group. Parameters *NH*, *NL*, N_2, *NP*, *OP*, and W_3 show smaller averages in the patient group than in the control group.

Summarizing, the "typical" face of patients with UTS is broader having a shorter nose with elevated base and tip. This contrasts with the results of an anthropometric study with 48 UTS patients published by Varrela and Vinka [1984]. These authors—who did not use a multivariate method—did not find any significant craniofacial differences between patients with UTS and normal females. The parameter *KP*, which describes the prominence of the chin and gives information about the often described retrognathia in UTS patients [Danhiez, 1970; Filipsson, 1965; Jensen, 1974, 1985; Kollmann, 1987; Leiber and Olbrich, 1963; Spiegel et al., 1971] does not occur in our discriminant function $\hat{D}^*$. Two reasons seem to be conceivable for this: either this parameter is relatively unimportant for discrimination or—what seems more likely to us—there is such a high

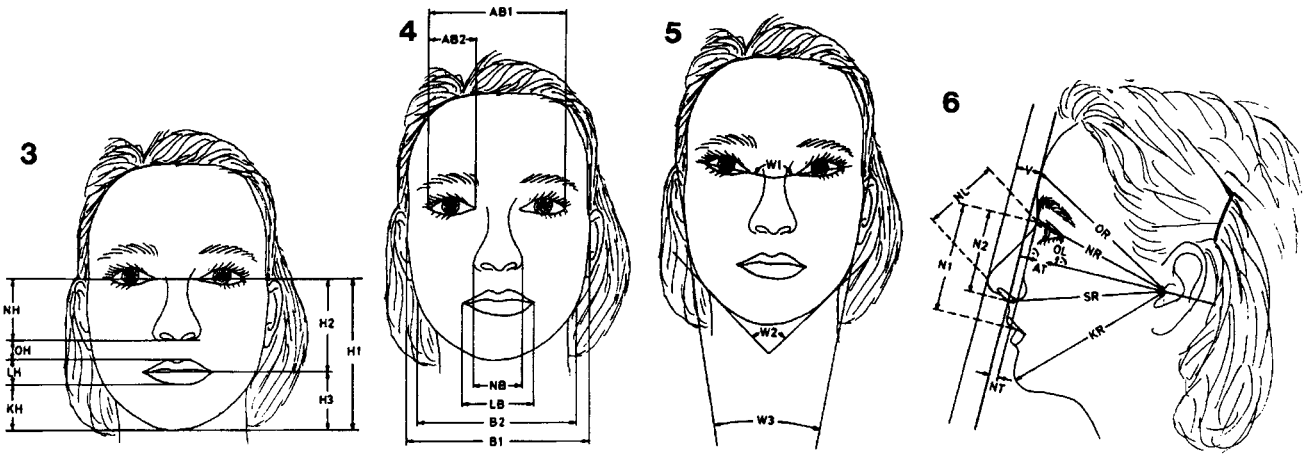

Fig. 3. Heights taken from the portrait photographs.

Fig. 4. Widths taken from the portrait photographs.

Fig. 5. Angles taken from the portrait photographs.

Fig. 6. Parameters taken from the profile photographs.

TABLE VII. Twenty-Nine Parameters Available for the Discriminant Analysis

Pos.	Abbreviation	Definition
1	H_1	Endocanthion—Gnathion
2	H_2	Endocanthion—Lip fissure
3	H_3	Lip fissure—Gnathion
4	*NH*	Endocanthion—Subalare
5	*OH*	Subalare—Upper edge of upper lip
6	*LH*	Upper edge of upper lip—Lower edge of lower lip
7	*KH*	Lower edge of lower lip—Gnathion
8	B_1	Bizygomatic diameter
9	B_2	Bigonial diameter
10	*LB*	Lip-width
11	*NB*	Bialare diameter
12	AB_1	Outer biorbital diameter
13	AB_2	Av. between right and left width of palpebral fissure
14	W_1	Angle of the eyes
15	W_2	Angle of right and left lower jaw tangents
16	W_3	Angle of right and left zygomatic-gonial straight-lines
17	Q_1	Ratio 1 (portrait)
18	Q_2	Ratio 2 (portrait)
19	Q_3	Ratio 3 (portrait)
20	Q_4	Ratio 4 (portrait)
21	N_2	Nasion—Subalare
22	*NL*	Nasion—Pronasale
23	*OL*	Incisura ant. of the ear—Exocanthion
24	*NHG*	Elevation of the nose baseline
25	*NP*	Prominency of the nose
26	*NT*	Nasion—Profile-line
27	*AT*	Exocanthion—Profile-line
28	*OP*	Prominency of the upper jaw
29	*KP*	Prominency of the chin

correlation with other variables within the function that *KP* had been eliminated in the analytical process.

In addition to the procedure described in the present paper a photographic technique was used to document the typical facial changes attributable to the syndrome. To this end two overlay photographs [Galton, 1883; Kaiser, 1988; Leiber, 1976] of all subjects in each of the two groups were produced (Figs. 9, 10). For the overlay photograph of each group the individual photographs of all subjects were projected one over the other. Both overlay photographs were compared between the patient group and the normal female group, showing clearly visible phenotypic differences, thus confirming the results of the discriminant analysis.

DISCUSSION

Because the chromosomal analysis is a reliable diagnostic method for clinical syndromes we were less interested in the development of a new diagnostic method but rather in the demonstration of the discriminant analysis as an excellent method for documenting typical anomalies associated with clinical syndromes.

The results of this multivariate technique were so encouraging that its application appears useful also in other anthropometric studies. Most studies in this field are concerned with comparisons of averages of individual variables only [Filipsson, 1965; Hughes et al., 1986; Ikeda et al., 1982; Jensen, 1985; Sandor et al., 1974].

The quantity and quality of anomalies of all variants of the UTS without X-monosomy could not be investigated in our study because there were only few patients with the same karyotype. These numbers were too small to find any phenotype regularity associated with a peculiar karyotype.

Since genetic patterns are related to morphological patterns, future studies may demonstrate to which extent the various chromosome types (non-X-monosomy)—which also can cause UTS—influence the phenotype of the patients. For this subtle investigation of the correlation between karyotype and phenotype the discriminant analysis in combination with photographic-anthropometric techniques seems very promising since there are hints in this direction found by other investigators [Allanson et al., 1993; Ferguson-Smith, 1965; Sarkar et al., 1983].

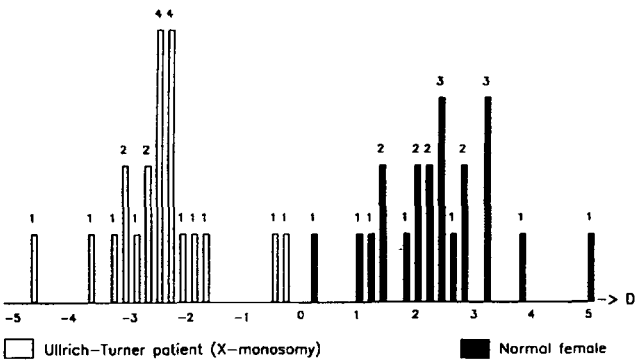

Fig. 7. Classification of subjects.

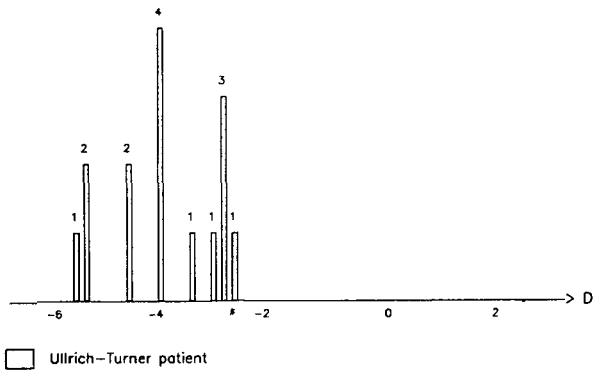

Fig. 8. Classification of UTS patients without X-monosomy.

Method and results reported in the present paper may be criticized in so far as some of the UTS patients have already had many years of hormone therapy, others only months or weeks. Some patients were even without any therapy when they were photographed. The aim of the hormone therapy was to increase height. Hormones given were either oxandrolone, an anabolic steroid, or human growth hormone. After this therapy an oestrogen-gestagen-therapy followed to develop the secondary female sexual attributes and "normal" monthly menstruations. Because up to now we do not have any information about the effect these hormones may have upon the phenotype of the syndrome, we cannot estimate its influence upon the results of our study. We do not believe that hormone therapy has camouflaged the specific anomalies of the UTS patients because both groups, the X-monosomy group and the UTS group with various chromosomal constellation, led to a 100% correct classification.

We chose to take measurements from standardized photographs, because this quick, simple and non-invasive technique "conserves" the whole face and may enable further comparisons, e.g., with other syndromes or new measurements.

It does not seem likely that measurement-precision and reliability—under standardized photographic conditions—differ from those of directly taken measurements. Ward and Jamison [1991] showed that in general the magnitude of error of craniofacial variables appeared to be quite low. According to them the most important factor affecting precision and reliability would appear to be the size of the measurement itself and the ease with which anatomical landmarks can be identified. For this purpose we consider the photographic technique used in our study to be at least as precise as direct measurements with the intrinsic limitations of the instruments used for the rounded contours of the face.

Fig. 9. Overlay photography of the control group.

Fig. 10. Overlay photography of UTS patients with X-monosomy.

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APPENDIX

With a total number of m variables available, the step-wise procedures in discriminant analysis either build up a model by adding a new variable at each step (step-up analysis) or delete one (step-down analysis) according to the decreasing or increasing importance, respectively, of the variable for the separation of the two groups of subjects. The assumptions underlying discriminant analysis are that the m-dimensional observational vectors (one from each subject) have an m-dimensional Gaussian distribution and that the two variance/covariance matrices are homogenous. For the present data these assumptions were considered to be approximately fulfilled. At least, all variables are quantitative although those constructed as quotients have slightly unsymmetrical distributions. In our analysis, inclusion or deletion of the individual variables was determined by the critical F-values $F_{IN} = F_{OUT} = 2.0$.

The number $m \leq 29$ of variables defined to form the original model was considered to be the maximal feasible number of such variables in the light of only $n = 42$ observational vectors. On the other hand, and when using the step-down procedure, the resulting $42 - m - 1 \geq 12$ degrees of freedom for the estimation of the error variance were considered just sufficient for the purpose.

Any discriminant function $\hat{D}^*$ estimated from the values of two particular groups of subjects presents an optimal means of separation between just these two groups of subjects. Therefore, in general each first estimate of D has to be confirmed by the values from two new groups of subjects. As mentioned under RESULTS, in the present example, this confirmation was established by the successful application of $\hat{D}^*$ to the group of the 15 patients without X-monosomy.

The discrimination contribution of the individual variables to the separation of the two groups is measured by their so-called "standardized canonical discrimination function coefficients"; the larger these coefficients, the more important the contribution. The overall discrimination is measured by Wolks' λ; the smaller λ, the better the separation.